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# Wound Care in Immunobullous Disease

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Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/intechopen.71937>

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## Abstract

The chapter introduces the steps to achieving proper wound care in immunobullous disease. It describes the clinical characteristics and nature of “wounds” formed in pemphigus versus pemphigoid diseases. Namely, pemphigus diseases typically result in acantholysis in the epidermis and the formation of flaccid blisters. In contrast, bullous pemphigoid presents with basal keratinocyte hemidesmosomes in the dermoepidermal junction, which results in a split at the dermoepidermal junction and clinically forms tense blisters. Therefore, there is a separate protocol for treating the wounds in each of these diseases, which must take additional patient specific factors into consideration.

**Keywords:** wound, care, wound healing, wound dressing, immunobullous disease, bullous pemphigoid, pemphigus vulgaris, immunosuppressant

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## 1. Introduction

Patients suffering from immunobullous disease have open wounds with a tendency to develop new blisters, which presents a unique problem when addressing wound care. These patients also have fragile skin limiting the use of adhesives. Immunosuppressant treatments increase infection risk and also prednisone slows wound healing but is needed to treat the disease. Therefore, there are many complexities surrounding proper wound care specific to these patients.

Clinical experience has shaped the steps to achieving wound care in immunobullous disease, but more research must be conducted to determine the best wound dressings for this critical patient population. While there are many similarities in the wound care of the pemphigus versus pemphigoid family, the differences in the nature of wounds formed in each of these diseases, calls for a unique plan.

## 2. Introduction to pemphigus

Pemphigus is a group of autoimmune blistering diseases of both the skin and mucosa, which is caused by the loss of cell to cell adhesion of keratinocytes which leads to intraepidermal blisters [1].

The classic forms are pemphigus vulgaris and pemphigus foliaceus. Pemphigus vulgaris most frequently presents with mucous membrane erosions (see **Figure 1**). Additionally, more than half of the patient population will also have cutaneous blisters and erosions. These blisters form in the deeper portion of the epidermis, directly above the basal cell layer. Pemphigus vegetans is a variant of pemphigus vulgaris that occurs as a result of polymicrobial superinfection of lesions [2].

In contrast, patients with pemphigus foliaceus only have cutaneous involvement, and lack mucosal lesions. The splits occur in the superficial part of the epidermis, mostly in the granular layer. Pemphigus erythematosus and fogo selvagem are localized and endemic variants of pemphigus foliaceus [3].

Paraneoplastic pemphigus was recently recognized as a disease distinct from the classic forms of pemphigus. These patients have a known or occult neoplasm, commonly of lymphoid tissue. Paraneoplastic pemphigus also features painful, severe oral and often conjunctival erosions [1].

Aside from the three classical cases are other less prevalent versions. IgA pemphigus is characterized by IgA (as opposed to IgG) autoantibodies directed against keratinocyte cell surfaces and can either be the intraepidermal neutrophilic type (IEN) which forms pustules throughout the entire epidermis, or the subcorneal pustular dermatosis (SPD) type, with pustules primarily in the upper epidermis [1].



**Figure 1.** Patient with oral lesions in pemphigus vulgaris.

### 3. Pathogenesis of pemphigus

All forms of pemphigus are a result of acantholysis, or the separation of keratinocytes from one another. The first step in this disease process is the dissolution of the intercellular substance, which leads to the separation of desmosomes. This results in the formation of a cleft within the epidermis, which expands to become bulla [1].

In every form of pemphigus, there are intercellular autoantibodies against keratinocyte cell-surface antigens, which are circulating and skin fixed. 80% of patients with active disease have circulating intercellular antibodies, and their titer usually correlates with disease activity. 90% of patients have tissue-fixed intercellular antibodies present in lesions and adjacent healthy skin. While the most prevalent antibodies are IgG, there are also frequently deposits of IgM, IgA and the complement protein C3. Since intercellular antibodies are uncommon when patients do not have pemphigus, they are very useful in making a diagnosis [1].

There is evidence that these intercellular antibodies are pathogenic. First of all, they are able to induce the histological changes of pemphigus (acantholysis) in organ cultures of human skin, and induce clinical and histologic lesions of pemphigus when passively administered to neonatal mice. Further studies reveal that placental transfer of maternal autoantibodies can induce transient lesions of the disease in newborn babies of women with active pemphigus vulgaris. Specifically absorbing out antibodies against desmoglein 1 or desmoglein 3 has been shown to prevent the passive transfer of disease in mice with pemphigus [4].

In pemphigus, the intercellular antibodies are directed against many keratinocyte cell-surface antigens, including desmoglein 1 and desmoglein 3. Both of these molecules are desmosomal transmembrane proteins in the cadherin family. The pathogenic antibodies against these proteins attack the portion of the protein that is expressed on the external surface of the cells and multiple epitopes on the same molecule can be targeted. In pemphigus vulgaris, intercellular antibodies are predominantly directed against desmoglein 3 and less often against desmoglein 1. However, in pemphigus foliaceus, the antibodies are mostly directed against desmoglein 1. Serological analysis has proposed that antibodies are also directed to other antigens, which was confirmed when pemphigus like lesions were induced in mice given intercellular antibodies not directed against desmoglein 1 or 3 [5]. It was observed that these additional antigens included acetylcholine receptors on keratinocytes.

Additionally, the subclass of the antibody response seems to dictate whether intercellular antibodies cause clinical disease. While IgG1 antibodies against desmoglein 3 are present in equal frequency in individuals with or without pemphigus vulgaris, IgG4 antibodies are almost exclusively present in patients with active disease [4]. Similarly, IgG1 antibodies against desmoglein are present in both individuals with or without endemic pemphigus and with or without active. It is believed that in endemic pemphigus, an unknown environmental agent might trigger the production of non-pathogenic IgG1 antibodies against desmoglein 1. However, the appearance of a clinical disease might be triggered by the presence of an HLA susceptibility gene required for the production of a pathogenic IgG4 response [4].

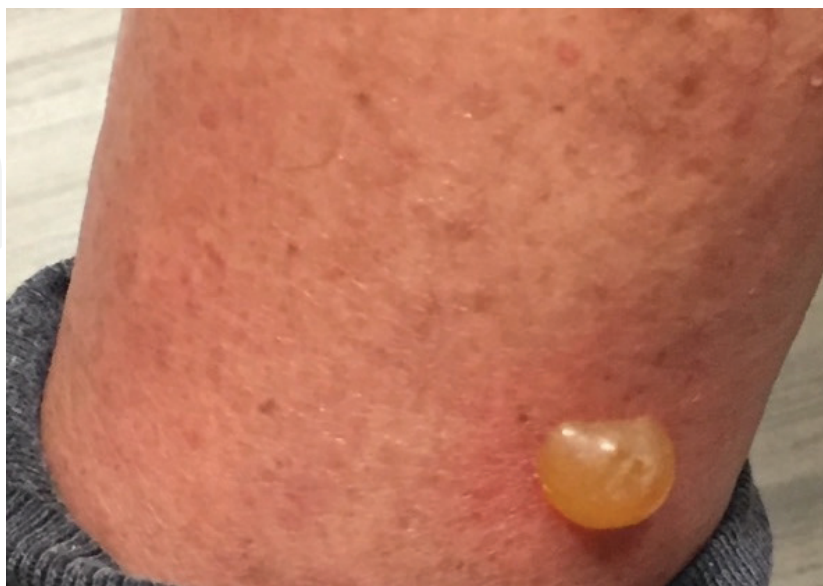
The exact process by which intercellular antibodies cause loss of cellular adhesion is not yet elucidated, though it does seem that the subclass of IgG response plays a role. There are various theories surrounding the exact mechanism. It is possible that the antibodies either physically block adhesion sites on desmoglein or on other adhesion molecules, or maybe they interfere with their structure or other functions or with the assembly of desmosomes. It is also possible that the antibodies stimulate release of proteolytic enzymes. In staphylococcal scalded skin syndrome, which is caused by a toxin that binds to and cleaves desmoglein 1, patients form blisters similar to those caused by pemphigus foliaceus [6]. Finally, one last possibility of the mechanism is that the antibodies trigger a signaling event which leads to reorganization of the cytoskeleton of keratinocytes, and causes the affected cells to shrink, pull away, and separate from adjacent keratinocytes [6].

#### 4. Introduction to pemphigoid

The pemphigoid group can be broken down into bullous pemphigoid, mucous membrane (cicatricial) pemphigoid, as well as epidermolysis bullosa acquisita.

Bullous pemphigoid is the most prevalent subepidermal blistering disease of the skin. It is most common in the elderly and is correlated with significant morbidity. The typical presentation is a generalized bullous eruption (**Figure 2**), but it frequently varies in the early stages of the disease. In this disease, patients typically make autoantibodies against two components of hemidesmosomes, which are the junctional adhesion complexes found in skin.

Mucous membrane pemphigoid is a very rare autoimmune subepithelial blistering disorder that has several notable features. It typically involves the mucosae, follows a sustained course, and tends to scar the affected areas. This disorder is a “disease phenotype” that encompasses a heterogeneous group of blistering disease, which tend to affect mucosal surfaces. Most patients



**Figure 2.** Patient with bullous pemphigoid with intact bulla on lower leg.





**Figure 3.** Patient with epidermolysis bullosa acquisita with mucosal lesion.

have linear deposits of immunoglobulins and/or complement components along the epithelial basement membrane zone of the skin and mucosae. There are classically low levels of circulating anti-basement membrane autoantibodies detected in the serum of some patients, at a low titer. This disease is recurrent and progressive and can have serious complications. If atrophic scarring and fibrosis affect the conjunctivae, it can ultimately lead to blindness [7].

Epidermolysis bullosa acquisita (EBA) is also a very rare disease. It is an acquired subepidermal bullous disease in which the patient has autoimmunity to type VIII collagen, which is the major component of the anchoring fibrils of the dermal-epidermal junction. Patients vary in the clinical presentation of this disease; some patients have a mechanobullous disorder that resembles dystrophic epidermolysis bullosa, while others have symptoms similar to bullous pemphigoid or mucous membrane pemphigoid [8] (**Figure 3**).

## 5. Pathogenesis of pemphigoid family

Bullous pemphigoid is immune-mediated and linked to a humoral and cellular response directed against two isolated self-antigens: BP antigen 180 (BP180, BPAG2 or type XVII collagen) and BP antigen 230 (BP230 or BPAG1e). BP antigen 180 is a transmembrane protein with a large collagenous extracellular domain. BP 230 is a cytoplasmic protein that is a member of the plakin family. Both of these antigens are components of hemidesmosomes, which are critical for epithelial-stromal adhesion in stratified and other complex epithelia [1].

Mucous membrane pemphigoid presents with mucocutaneous lesions, which are believed to be a result of when autoantibodies bind to the basement membrane zone of stratified epithelia of mucosa and skin. These autoantibodies bind to extracellular antigenic sites located within the anchoring filament zone, rather than within the hemidesmosomal plaque. However, the exact

Autoantigens	Location
BPAg2 (BP180)	Hemidesmosome/Lamina lucida (transmembrane)
BPAg1 (BP230)	Hemidesmosome (intracellular)
Integrin subunits $\alpha 6/\beta 4$	Hemidesmosome (transmembrane)
Laminin-5 (laminin-332/epiligrin, $\alpha$ -3, $\beta$ -3, $\gamma$ -2 chains)	Lower lamina lucida
Laminin-6	Lower lamina lucida
Type VII collagen	Lamina densa/Sub-lamina densa

**Table 1.** Autoantigen in bullous pemphigoid, mucous membrane pemphigoid & epidermolysis bullosa acquisita and their localization within the dermis/epidermis junction (DEJ).

pathogenicity of autoantibodies involved in this disease has not been fully elucidated. In some patients with mucous membrane pemphigoid, NC16A domain-specific T cells were identified. Additionally, it was found that when patients have ocular disease, there is increased expression of collagen-binding heat shock protein 47 (HSP47) and TGF-B1 by conjunctival fibroblasts that might be associated with conjunctival scarring [7]. There are four subgroups of mucous membrane pemphigoid patients, based on the reactivity profile of patients’ autoantibodies (**Table 1**).

Epidermolysis bullosa acquisita is also an immune-mediated disease. These patients have tissue-bound and circulating autoantibodies to a structural component of the dermal-epidermal junction. There is tissue injury where these antibody–antigen complexes are found. The role of these autoantibodies in causing disease has been reaffirmed by in vitro and in vivo animal models of the disease [8].

## 6. Wounds

### 6.1. Wounds in pemphigus vulgaris

Pemphigus vulgaris typically presents with painful, non-healing ulcerations in the mouth. These blisters rupture soon after forming and leave an ulcerated area. There are usually many ulcerations that are superficial and irregular in shape, which arise from mucosa of healthy appearance. The lesions most commonly form on the buccal and labial mucosa, the palate and the tongue. However, it is possible for any mucosal surface to be involved. In contrast to the oral lesions of aphthous stomatitis or viral infections that heal in a matter of days or weeks, these ulcerations usually will not heal on their own [9].

Due to the rarity of the disease, there is on average a 10-month delay in diagnosis and pemphigus only considered when lesions have remained for weeks to months, in spite of antibiotic, antifungal or antiviral therapy [10]. If there are multiple, non-healing oral ulcers that persist for longer than a month, pemphigus should be considered.

As the disease progresses over the following weeks to months, lesions begin to appear on the skin and with symptoms signifying nasal and esophageal involvement. Sometimes, the disease begins to manifest with skin lesions. The skin lesions begin as small blisters that are filled with

a clear fluid that arises from seemingly normal skin. The blisters are usually flaccid, since the overlying epidermis is thin and cannot sustain much pressure. Since the blisters are so fragile, they usually rupture in several days and form coin sized erosions often with a collarette of epidermis. The lesions are most frequently found on the scalp, upper chest and back. They are more commonly found on the medial or central part of the torso rather than the sides. The face and neck are also commonly involved, but lesions can appear on any surface covered by stratified squamous epithelium. It is important to also check the per inguinal areas, the pharynx and larynx, manifested by nasal congestion and morning mucous discharge. A recent systematic study showed that 49% of patients had symptoms of laryngeal or nasal involvement, or both [11].

If the lesions are left untreated, the bullae and erosions spread. As with burns, widespread lesions can be complicated by severe infection or metabolic disturbance, or both, leading to death. Prior to the development of systemic corticosteroids, about 75% of patients who develop pemphigus vulgaris died within a year [11]. However, improved diagnostic techniques now permit the recognition of subtler forms of disease. The severity of pemphigus can vary widely. There are milder forms that regress spontaneously and the progression of even the most severe forms can almost always be reversed with appropriate treatment.

Following treatment, lesions heal with crusting followed by reepithelization. While there is no scarring, there can be residual hyperpigmentation at sites of former lesions. The hyperpigmentation will usually disappear over several months. At some point, these patients can enter a phase of partial or complete remission. In partial remission, they can be maintained, lesion-free with minimum (<15 mg per day prednisone) doses of corticosteroids. In complete remission, they are lesion free for 2 months and do not need any therapy [9].

A longitudinal study was performed, which assessed the outcome of 40 patients. It showed that half of the patients reached complete and long-lasting remission after 5 years and three quarters reached the same end point after 10 years [9].

Despite the complete or partial remission, it is fairly typical for flares of disease activity to occur. The flare can present with new lesions and itching. There are many factors that are thought to possibly trigger a flare, including arthropod bites, hospitalization, dental work, exposure to the sun, cutaneous trauma, infection, as well as other forms of physical or emotional stress [9].

The wounds in pemphigus vegetans are very similar to pemphigus vulgaris, however, healing is accompanied by vegetating proliferation of the epidermis. The lesions present in intertriginous areas of the skin, including the axilla of the arm, the groin and the inframammary area and scalp. Due to the nature of the location of these lesions, they are often secondarily infected, which further slows the healing.

## 6.2. Pemphigus foliaceus

The wounds in the superficial forms of pemphigus differ greatly from those in pemphigus vulgaris. These diseases present in such a superficial layer of the skin, that there is not enough tissue to trap fluid and allow for blister formation. The lesions present as many pruritic, crusted, coin-sized patches on the upper torso, face and scalp (**Figure 4**). The skin had previously been healthy and the lesions have been described as “cornflakes”. These superficial crusts can be removed fairly easily, and will leave behind superficial erosions. If the lesions are not treated, they will





**Figure 4.** Patient suffering from pemphigus foliaceus on back.

not heal and will only increase in number. In more severe cases of superficial pemphigus, the lesions can appear to merge and present similarly to exfoliative erythroderma, where the entire skin surface is affected. Oral involvement is uncommon in superficial forms of pemphigus.

The two clinical variants of pemphigus foliaceus, pemphigus erythematosus and fogo selvagem also vary in their specific presentation. Pemphigus erythematosus tends to resemble lupus erythematosus in that it typically presents on the face in a butterfly distribution. In all forms of pemphigus, there are tissue-fixed intercellular deposits of antibodies. However, in pemphigus erythematosus, there are also often granular deposits of immunoglobulin or complement or both at the dermal-epidermal junction. As such, it is speculated that pemphigus erythematosus might be a crossover syndrome between pemphigus foliaceus and discoid lupus erythematosus. However, it is important to note that granular deposits of immunoglobulin or complement or both are not uncommon in normal sun exposed facial skin [1].

Fogo selvagem is histologically and immunologically identical to pemphigus foliaceus. The predominant difference is that it occurs in only certain rural areas in the world. Treatment for pemphigus foliaceus is similar to that for pemphigus vulgaris, requiring similar doses of drugs to control the disease. However, the prognosis is better for pemphigus foliaceus, due to the fact that the lesions are more superficial and there is therefore a smaller risk of infection, fluid loss and metabolic disturbance [1].

### **6.3. Wounds in bullous pemphigoid**

Bullous pemphigoid has many different forms of its cutaneous presentation. There is a non-bullous, prodromal phase of the disease, the signs and symptoms are not always specific

to bullous pemphigoid. For example, there can be mild to severe intractable pruritus alone or in association with excoriated, eczematous, papular and/or urticarial lesions that may remain for several weeks or months. At this phase, the only sign of the disease may be these nonspecific cutaneous findings [12].

At the bullous stage of bullous pemphigoid, the patient develops vesicles and bullae on an urticarial base. They commonly also have urticarial and infiltrated papules and plaques, which can present in an annular or figurate pattern. Unlike in pemphigus, these blisters are tense. They range from 1 to 4 cm in diameter, are filled with a clear fluid and persist for several days (**Figure 2**). After they pop, they become eroded and crusted areas. Sometimes, the blister fluid becomes blood-tinged. Commonly, the lesions have symmetrical distribution patterns and they often present on the flexural aspects of the limbs and lower trunk, including the abdomen [12].

There are residual post inflammatory changes ranging from hyper- to hypopigmentation. Occasionally, milia appear as well (**Figure 6**). In 10–30% of patients, there is involvement of the oral cavity. Rarely, the mucosae of the eyes, nose, pharynx, esophagus and anogenital region are affected. Additionally, in about half of the patients, there is a peripheral blood eosinophilia.

#### 6.4. Wounds in mucous membrane pemphigoid

The oral and conjunctival mucosae are the two most commonly involved sites for patients with this diagnosis. However, it is still possible for the disease to first appear in and affect any mucosal site, including the external genitalia, the anus, the upper aerodigestive tract and/or the esophagus. Around 85% of patients with mucosal membrane pemphigoid have oral involvement and it is possible that the oral cavity is the only site of disease activity [13].



**Figure 5.** Epidermolysis bullosa acquisita patient with post inflammatory hyperpigmentation in annular pattern on legs.



**Figure 6.** Patient with milia on wrist, following treatment for bullous pemphigoid.

Within the oral cavity, lesions often involve the gingiva, buccal mucosa, and palate. It is less common to see lesions on the alveolar ridges, the tongue and the lips [1] (**Figure 3**).

Frequently, mucous membrane pemphigoid in the oral cavity presents as desquamative gingivitis along with bleeding erosions and paresthesia. In this case, it is rare to see small intact blisters. Sometimes, periodontal ligament damage and the loss of teeth may occur as a result of chronic inflammation. In certain parts of the mouth, transient vesicles can lead to chronic erosions. This can occur on the palate and is accompanied with variable pain. When there are lesions on the tongue, they are found on the lateral and ventral surfaces. Adhesions may form in the area of the uvula and tonsillar fossae as well as between the tongue and the floor or the mouth. After the lesions heal, they may become white reticulated striations, which look similar to lichen planus [1].

When the conjunctiva is affected, this can lead to blindness. Often, the conjunctiva is the only site affected. In most cases, lesions occur in both eyes, although the disease can begin unilaterally as well.

At the start of ocular involvement, there is nonspecific, chronic conjunctivitis, with burning, soreness, foreign-body sensation or mucus production. This conjunctivitis can either go into remission or become exacerbated, where it will progress to subepithelial conjunctival fibrosis [1].

It is rare to see conjunctival vesicles or blisters on the tarsal conjunctiva. Chronic inflammation is detrimental to the eyes and can lead to progressive scar tissue formation, shortened inferior fornices, and symblepharon formation, which is adhesion between bulbar and palpebral conjunctival surfaces. Trichiasis, or inwardly angled eyelashes, and entropion, can also result

from conjunctival fibrosis. If the disease is not adequately controlled, trichiasis, entropion and xerosis (from scarring of lacrimal ducts) will lead to superficial corneal trauma, corneal neovascularization with subsequent corneal ulceration and blindness [7].

When the nasopharynx is involved, it is chronic and leads to extensive lesions of the upper aerodigestive tracts. The lesions lead to crusted ulcerations, epistaxis, fibrous adhesions between adjacent mucosal surfaces, and airway obstruction. When the pharynx is involved, there are typically ulcerations of the posterior or lateral pharynx and dysphagia. Laryngeal involvement is a potentially serious manifestation. It will present as hoarseness, loss of speech and can even lead to life-threatening stenosis, which requires tracheostomy [7].

While there is often dysphagia from the erosions of the esophageal mucosa, often esophageal disease can be asymptomatic. On the other hand, if there is chronic inflammation, it can lead to strictures and stenosis, with the associated dysphagia [7].

It is rare to see lesions on the genital and anal mucosa. However, when they appear, there are blisters and chronic erosions. In females, if there is progressive disease, it can lead to atrophic scarring and narrowing of the introitus. On the other hand, in male patients, adhesions can appear between the prepuce and the glans penis. When the anus is affected, it can result in anal scarring and in more severe cases, it can lead to stricture formation [7].

25–30% of patients with mucous membrane pemphigoid have skin involvement [7]. In this case, the lesions typically appear on the scalp, face, neck and upper trunk. These lesions differ from bullous pemphigoid in that they present as erythematous plaques, which lead to recurrent blister formation and erosions, with subsequent atrophic scarring. There are typically not too many lesions, but on occasion a patient can have bullous pemphigoid like clinical presentation [14].

In the Brunsting-Perry variant, skin lesions are only found on the head and neck region and mucosal involvement is typically minimal or absent. When the skin lesions are on the scalp, it can lead to scarring alopecia [33].

### **6.5. Wounds in epidermolysis bullosa acquisita**

The presentation of epidermolysis bullosa acquisita is typical for a non-inflammatory mechanobullous disease. Namely, these patients develop acral blisters that heal with atrophic scarring, milia and hyper or hypopigmentation (**Figure 5**). Cutaneous blisters and subsequent erosions appear within non-inflamed skin or on areas of scarring. They are more frequently serous, but can also be hemorrhagic. They are typically found in more trauma-prone surfaces, including the elbows, knees and dorsal aspects of the hands, feet, and toes. Up to 20% of patients do have scalp involvement and extensive non-healing erosions with scarring alopecia have been noted in some cases [1].

### **6.6. General principles of wound care**

Wound healing is a complex and active process that follows three consecutive phases. These include inflammation, tissue formation and tissue remodeling. In order for wound healing to be effective, there must be synchronization of not only cell–cell and cell-matrix interactions, but also interplay of cytokines to ensure successful communication among various processes.



The major players in this process include extracellular matrix proteins, cell surface receptors or integrins and growth factors. The extracellular matrix proteins have many functions, and bind directly to the cell surface receptors. As a result, they determine the effects of growth factors, such as TGF-beta, on cells [1].

While injured fetal tissue has the capacity to regenerate, or heal completely without fibrosis, injured tissue in children and adults still follows a reparative process, but can lead to fibrosis. There are many systemic diseases, including diabetes mellitus and atherosclerosis, as well as more local factors, such as pressure and infection, that can lead to chronic non-healing wounds [4].

When an injury occurs, it is critical to restore skin integrity and homeostasis. Therefore, the main goal of wound healing response is to quickly reform a functional skin barrier. The best wound healing response would be if there was complete regeneration of skin tissue and its adnexal structures. Ideally, original skin function and morphology would be completely restored. However, this is often not the final result of wound repair and there are variable responses in how skin tissue reforms [4].

### **6.7. Regeneration versus repair**

In wound healing response, a distinction must be made between regeneration and repair. The wound healing responses follows repair more than regeneration. In other words, the skin barrier is not restored to its pre-injured state, but rather leads to fibrosis or scar formation. Additionally, adnexal structures, including hair follicles, sweat and sebaceous glands, and components of the dermal extracellular matrix may not regenerate. As a result, there is a loss of normal skin function and impaired morphology [15].

Regeneration can occur during embryogenesis to injured fetal skin. It is able to heal completely without fibrosis. Research has indicated that fibromodulin, a small leucine rich proteoglycan, is thought to mediate scarless fetal skin wound repair [15]. It is thought that this process partly works via transforming-growth factor- beta modulation. A research study showed that when fibromodulin-/- mice were compared to wild type mice, they were found to have delayed wound closure and a large increase in scar size. When they were later administered exogenous fibromodulin, there was improvement in wound closure and scar size [15].

### **6.8. Effect of immune response on wound healing**

The immune system, and its major players, including neutrophils and macrophages hold a key role in wound healing. Inflammation influences the repair process and can affect the quality of the wound and the extent of scarring. Many repair models have shown that there is an inverse correlation between the strength of the inflammatory response and the ability to undergo regeneration. Namely, it appears that when the inflammatory immune response is greater, there is more inappropriate wound repair [16].



## 6.9. Insights from animals on the immune system and wound healing

Amphibians and fish are unique in their ability to regenerate anatomically complete and fully functional tissues and organs. Specifically, urodele amphibians (newts and salamanders) can regenerate a range of organs and tissues [17]. This occurs in a process in which there is dedifferentiation of cells at the site of amputation injury, followed by their proliferation to produce a blastema that finally reforms the missing tissue. It is postulated that the ability to regenerate is related to the fact that the regenerative response induces minimal inflammation. However, further investigation is needed to elucidate the role of inflammation in the regenerative response [1].

Furthermore, zebrafish are able to regenerate their entire caudal fin, even as adults, including the original pigment and color structures [18]. However, in this process, regeneration occurs in the presence of inflammation since there is an infiltration of myeloid inflammatory cells early on. When an experiment knocked out the gene responsible for myeloid cell development and the inflammatory response, there was no effect on fin regeneration [19]. Therefore, future research must examine whether there is a relationship between fin regeneration in zebrafish and the inflammatory response.

In mammals, such as mice and humans, the effects of inflammation on regeneration and repair have also been studied. In children and adults, wound repair results in scar formation. However, injured fetal skin is able to fully regenerate in a scarless manner [20]. It is noted that a major difference between fetal and post-natal skin is that there is a lack of significant inflammation in fetal skin post injury. Additionally, there is a difference in the extracellular matrix, cellular mediators, gene expression profiles as revealed by transplantation experiments, as well as unknown factors intrinsic to fetal skin [21].

There have been experiments using transgenic mice to learn more about wound healing. When mice were lacking nidogen 1, a basement membrane component, or TGF-beta, there was delayed wound healing [22]. Additionally, there was delayed wound healing in mice with a fibroblast-specific deletion of integrin B1, which binds extracellular matrix proteins, in mice that lack superoxide dismutase, an important antioxidant enzyme, or IL-6 in mice that lack Toll-like Receptor 3, and have a defective recruitment of neutrophils and macrophages [23]. When mice lack matrix metalloproteinases, which degrade extracellular matrix proteins, or when mice are deficient in Natural Killer (NK) or T Cells, there is accelerated wound healing [24].

## 6.10. Wound depth and wound healing

Different terminology is used to describe a wound, depending on its depth. Wounds are categorized as erosions when they only affect the epidermis. However, when the wound extends into the dermis, it is referred to as ulceration. Partial thickness wounds are when the epidermis and portions of the dermis are missing, and the ulcer extends into the mid dermis. In partial thickness wounds, adnexal structures remain. On the other hand, in full thickness wounds, the entire dermis is involved, and the wound extends into the subcutaneous fat. In these wounds, adnexal structures are lost as a source of keratinocytes necessary for reepithelization [1].

The extent to which the skin can repair or regenerate is dependent on the depth of the skin injury. For example, erosions are the least severe of the wounds mentioned above. When they heal, the entire epidermis is able to regenerate, and here is no scarring. On the other hand, ulcerations heal via a reparative, not a regenerative process, and are therefore associated with scar formation [1].

As mentioned above, in partial-thickness wounds, the preserved adnexal structures serve as a source of epithelial to repopulate the epidermis [25]. Specifically, epithelia from these structures and the wound edge migrate across the wound surface to provide full coverage.

However, in full thickness wounds, where adnexal structures are lost, the reepithelialization can only occur from the wound edges [26]. As a result, healing of full-thickness wounds includes contraction. While the mechanism of contraction in wound healing is not fully elucidated, it is believed that contraction may be mediated by mechanical or biologic factors, such as differentiation of fibroblasts into myofibroblasts. During contraction, there is centripetal movement of pre-existing tissue, rather than formation of new tissue.

#### **6.11. Cellular and molecular aspects of skin repair**

Numerous cell types interact during the repair response. These include cells that reside in the tissues, such as keratinocytes, endothelial cells, and fibroblasts, as well as hematopoietic cells that are recruited to the site of tissue damage. These cell types all interact during the three phases of wound repair [27].

#### **6.12. Inflammatory phase**

The first phase of wound repair is the hemostasis and inflammatory phase. When tissue injury occurs, there is extravasation of blood into the wound and eventual clot formation. The clot is comprised of collagen, platelets, thrombin and fibronectin. These factors release cytokines and growth factors that initiate the immune response [28].

Then, there is local activation of innate immune functions and chemoattraction. Both of these processes result in an early influx of polymorphonuclear leukocytes or neutrophils. Neutrophils destroy bacteria by releasing caustic proteolytic enzymes. Next, there is an invasion of blood monocytes, which differentiate into tissue macrophages. Activated macrophages clear the wound of dead neutrophils, bacteria and debris, as well as release many cytokines necessary for angiogenesis, such as VEGF, TGF-Beta, and platelet derived growth factor. As inflammation progresses, the number of neutrophils decline, while the number of macrophages increase [28].

#### **6.13. Proliferative phase**

The release of cytokines and growth factors is necessary for the initiation of the proliferative phase. In this phase, invading macrophages, fibroblasts and endothelial cells make up newly formed granulation tissue. Many proteins such as fibrin, fibronectin, vitronectin, collagen III and tenascin are components of the provisional extracellular wound matrix which enable cell

adhesion, migration and proliferation. There are also epidermal-mesenchymal interactions at the wound edge, which stimulate keratinocyte proliferation and migration, and ultimately lead to reepithelization [29].

#### **6.14. Remodeling (maturation) phase**

After epithelization is complete and cell proliferation and neovascularization stop, scar tissue forms and the wound enters the remodeling phase. This phase lasts several months and is described by a balance between the synthesis of new components of scar matrix and their degradation by proteases. The degree of balance between the two processes determines whether there is normal or abnormal scar formation. Abnormal scar formation includes atrophic scars, hypertrophic scars and keloids. The exact mechanism of how granulation tissue regresses and transforms into scar tissue is still not completely known [30].

In addition to the scar tissue formation, there is also regression of vascular structures, transformation of fibroblasts into myofibroblasts, substitution of provisional extracellular matrix with a permanent collagenous matrix and a final act of the inflammatory response. The exact mechanism of this step is still not known [31].

#### **6.15. Wound healing and aging**

There are two main mechanisms which are related to human aging. These include telomere shortening and DNA damage. When telomere shortening or dysfunction occurs, there is instability of chromosomes. In a study examining telomerase-deficient mice, impaired wound healing was noted. Additionally, when mice had increased activation of the transcription factor p53 within the epidermis, they developed an early aging phenotype of their skin and impaired wound healing [32].

#### **6.16. Wound healing and immunosuppressants**

Immunosuppressive therapy is used to treat immunobullous disease. Depending on the specific immunosuppressive treatment, wound healing is affected to different degrees.

Wound healing is a complicated process involving many different cells, hormones, cytokines, proteases and growth factors. Additionally, these can be broken into four phases: hemostasis, inflammation, proliferation and remodeling, which are each essential for adequate wound healing. Research demonstrates that immunosuppressive agents that are used in conditions such as organ transplant and IBD have been shown to impair the wound healing process [33] (Table 2).

#### **6.17. Several inflammatory mediators involved in the wound healing process are affected**

Immunosuppressants affect several inflammatory mediators involved in the wound-healing process. These include IL-2, IL-4, IFN-gamma, TNF, alpha, and GM-CSF. At the outset, IL-2 activates macrophages, T cells, NK cells and lymphokine-activated B cells and T cells. IL-4

Author(s)	Drug(s) under investigation	Type of study	Type of wound examined	Result
Burgos et al. [34]	Cyclosporine, tacrolimus, MMF, SLR, everolimus, prednisolone (in different combinations)	Retrospective	Abdominal wounds	Tacrolimus less likely to cause collections or bleeding ( $p < 0.05$ and $p = 0.02$ )  Lymphocoeles more common in mammalian target of rapamycin-inhibitor regimens ( $p = 0.012$ )
Valente et al. [35]	MMF, SLR	Retrospective	Abdominal wounds	Incidence of wound complications 2.4% (MMF group) compared with 43.2% (SLR group) ( $p < 0.0001$ )
Grim et al. [27]	SLR, MMF, steroid and tacrolimus (in different regimens)	Retrospective	Abdominal wounds	31.8% in the SLR group developed wound complications compared with 14.3% in the tacrolimus group ( $p = 0.0163$ )
Selman et al. [36]	Rituximab	Prospective	A linear dorsal incision in mice	The results yield that the wound healing significantly decreased ( $p < 0.05$ ) in Groups 2 and 3, which received Rituximab, as compared to control group.

**Table 2.** Role of immunosuppressive drugs in wound healing.

stimulates fibroblast proliferation early in the wound healing process and later on downregulates cytokine expression. IFN-gamma and TNF-alpha are both leukocyte chemoattractants. In addition, IFN gamma, along with GM-CSF, is a leukocyte activator [33].

**6.18. Modes of action of immunosuppressant drugs**

*6.18.1. Systemic steroids*

Systemic steroids are chemical modifications of natural glucocorticoids. The most commonly used systemic steroids include prednisone and prednisolone. To become active, prednisone is converted to prednisolone by modifying the 11-keto group to become an 11-hydroxyl group. The glucocorticoid activity of prednisone and prednisolone is 3–4 fold greater than hydrocortisone. Corticosteroids alter lymphocyte recirculation and create a transient lymphocytopenia. They also induce lymphocyte death. The most important immunosuppressive effect of corticosteroids is inhibiting cytokines, which further prevents T cell activation [37].

*6.18.2. Azathioprine*

Azathioprine is the 1-methyl-4-nitro-5-imidazolyl derivative of 6-MP. AZA and its metabolites suppress intracellular inosinic acid synthesis, which interferes with intracellular purine synthesis. This drug leads to a reduction in the number of circulating B and T lymphocytes, which results in decreased immunoglobulin production and reduced IL-2 secretion [33].

Stolzenburg et al. studied the effect of Azathioprine on anastomotic healing in rats. There were 48 Wistar rats divided into groups of four per cage, then randomized into three groups receiving one daily dose of placebo, low dose, Azathioprine, and high dose Azathioprine. There were no significant differences in wound healing between the three groups [33].

#### 6.18.3. *Mycophenolate mofetil*

Mycophenolate mofetil (MMF) is an ester of an old drug, mycophenolic acid. It is an anti-metabolite agent that interrupts purine metabolism in T and B lymphocytes. It inhibits the generation of cytotoxic T cells and the rejection of allogeneic cells. Research has shown that it can suppress the formation of antibodies against alloantigens in a chronic rejection model and that it can abolish the formation of antibodies against xenogeneic cells [33].

There have been some animal studies performed to look into the effect of mycophenolate mofetil on the healing of left-sided colon anastomosis in Sprague-Dawley rats. This study showed that MMF inhibits injury induced reparative proliferation of colonic mucosal cells. The bioavailability of MMF in humans is nearly 100% and pharmacokinetic measures are similar in humans and rats [33].

#### 6.18.4. *Rituximab and wound healing*

Rituximab binds to the CD20 antigen found on the surface of all B-lymphocytes, it lyses the cells and activates complement. In all cases in which rituximab is given, there is a rapid decrease of circulating B-cells. B-cell recovery does not begin until 6–9 months after completion of treatment [38].

Rituximab delays wound healing in male mice and that further research is needed to study the direct effects of the drug on wound healing in humans [38].

There is a clear correlation between immunosuppressive agents, inflammatory mediators and the wound-healing process. This complicates treatment of autoimmune bullous diseases where immunosuppressant therapy is required to treat the underlying condition [33].

## 7. Wound dressings

Currently, there are many different wound dressings available. However, the specific type of dressing depends on characteristics of the wound. While clinical trials have examined the efficacy of different dressings for a variety of wounds, clinical experience has ultimately shaped most of the recommendations.

The commonly accepted mechanism of action of wound dressings is to support wound healing by acting as a barrier between the wound and the environment, by preventing drying of the tissue or autolytic debridement. There are some dressings which actually interfere with cellular and molecular mechanisms of the wound microenvironment, and counteract mechanisms that are considered incompatible with wound repair [39].



## 8. Role of growth factors

Growth factors help to regulate cell function during wound repair. Therefore, topical application of many growth factors can modify and even accelerate wound repair.

Platelet-derived growth factor (PDGF-BB) is the first and only recombinant growth factor to be effective and approved for the topical treatment of diabetic foot ulcers [40]. Currently, there is promise in the use of perilesional injections of granulocyte-macrophage colony-stimulating factor (GM-CSF). Wankell et al. showed that in transgenic mice, where an antagonist of GM-CSF was overexpressed in the epidermis, delayed wound healing was observed [41]. However, further studies must be conducted to further explore the efficacy of this treatment.

There is promise in a combined molecular and genetic approach. Ideally, genetically modified cells would synthesize and deliver the desired growth factor in a time-regulated and locally restricted manner to the wound site. This would overcome some of the limitations that are faced in the local application of recombinant growth factors [42].

## 9. Composition of a dressing

The exact composition of a dressing is an important factor in the decision process. It should be made of an inert material, which will not shed fibers or compounds into the wound. If the material is not inert, a foreign body or irritant can enter the wound and lead to an immune response.

A critical aspect of a wound dressing is the capacity to maintain a moist environment. Moisture assists the reparative process, by suppressing tissue desiccation and crust formation. If a wound is left to dry, a scab or eschar will form. This specifically occurs in the superficial dermis, which actually becomes integrated into the scab itself [1].

In 1962, there was a study conducted by George Winter that looked at moist wound healing. It demonstrated a 30% greater benefit of occlusive dressings versus air drying of wounds. There have been subsequent studies since Winter's work that further demonstrate the benefit of moist wound healing by occlusive dressings [31].

Winter and Scales conducted studies examining the effects of leaving wounds uncovered. They found that air dried wounds developed thicker scabs and reepithelialized at a slower rate. This is due to the fact that when the wound is air dried, the regenerating epidermis must migrate deeper below the dry fibrous tissue to a region of moisture where live cells survive. It is only in such an environment where epidermal cells are able to move toward bridging the defect of the wound. The thickness of the wound correlates with the deepness of the migration of the regenerating epidermis. The thickness of the wound in addition to the continuing loss of dermis and collagen and a reduction in adnexal structures, contributes to the depth of the scars and to a worse cosmetic outcome [31]. Therefore in the case of pemphigus and pemphigoid, the superficial depth lends itself to compute healing without scarring. The

predictable depth of these erosions is intraepidermal in the case of pemphigus vulgaris and at the dermis epidermal junction in bullous pemphigoid.

Furthermore, there are many endogenous factors that are essential for proper wound healing that are found in fluid from occluded acute cutaneous wounds that may be more available in a moist environment [31].

Finally, it is believed that moist wound healing environment has the ability to confer an electrical gradient between the wound and normal skin. Following injury of the skin, there is an internal battery and a current flow created until drying of the wound occurs. By maintaining the moisture, the electrical gradient may promote epidermal cell migration between the wound and the surrounding skin [39].

## 10. The role of oxygen in wound healing

The requirement for oxygen differs based on the stage of wound repair. Studies have shown that the oxygen requirement is low in the early wound repair stages. Following acute injury, there is a disruption of blood flow from clotting that prevents exsanguination. This leads to a temporary but extreme hypoxia, which is a signals the migration of keratinocytes and fibroblasts as well as the initiation of angiogenesis [43].

Additionally, studies have shown that hypoxia upregulates proliferation and production of TGF-Beta by dermal fibroblasts. Then, TGF-Beta stimulates production of extracellular matrix molecules. It is also noted that hypoxia allows keratinocytes to migrate better along keratin and fibronectin, and that low oxygen levels promote angiogenesis in the acute wound [43].

Therefore, the use of semipermeable dressings has been promoted to allow the appropriate oxygen tension for wound repair to proceed quickly. When acute wounds have been allowed to heal under occlusion, they have shown accelerated healing, greater resistance to breaking open, as well as better cosmetic outcomes than those that heal open to the air [44].

## 11. Traditional wound dressings

Traditionally, wound dressings have been composed of natural, synthetic or partially synthetic materials. Cotton, silk, linen or cellulose-based substances are naturally occurring materials that have been produced in many combinations to maximize clinical usefulness. Today, the basic cotton gauze dressing is composed of cotton plus cellulose acetate. The cellulose acetate is added to enhance the absorbency [1].

Different manufacturers incorporate various substances into the fabric. These include white petrolatum and other ointments, including paraffin wax (Vaseline gauze, aquaphor gauze), and can also include antibacterials such as povidone-iodine, sulfadiazine, bismuth, framycetin and chlorhexidine. Medicated dressings are frequently used for malodorous wounds such

as chronic ulcers, and are made of rayon, nylon or gauze. Activated charcoal cloth with or without antibacterial silver salt is also used for exudate absorption as well as odor control [1].

Traditional wound dressings are placed immediately against the wound bed and have multiple advantages. These include the advantage of having less chance of adhering to the wound. The main disadvantage of this type of dressing is the potential for maceration of the wound and surrounding skin if the dressing stays in place for an extended period of time [39].

While traditional dressings are relatively inexpensive and readily available, they require frequent replacement. This can be time consuming for both the patient and the medical staff. Therefore, traditional dressings are potentially costly in terms of the time required for health-care personnel [44].

## **12. Technique for most conventional dressings**

Currently, most dressings are layered and either qualifies as “pressure” or “non-pressure” dressings. A layered dressing is usually composed of three parts. There is a contact or interface layer, which is typically a non-adherent, fluid permeable material, which makes direct contact with the wound. Next, there is the absorbent layer. This is normally a cotton pad, gauze or other material. It is placed directly on top of the contact layer to “wick-in” and retain wound exudate. This also allows the dressing to mold to the shape of the wound. Finally, there is an outer layer or wrap, which is often tape or another banding material, such as a self-adhesive bandage. Its purpose is to retain the underlying layers. It is essential that each layer is placed in close approximation to the one before it, without air pockets. Each layer should also increase in size and degree of overlap from the wound to the outermost layer [1].

## **13. The use of antimicrobial agents in wound dressings**

There is debate regarding the usefulness of topical antimicrobial agents for cutaneous wounds. It is believed that in the absence of infection, a topical antimicrobial is not necessary as well as the wound is taken care of well. However, there is evidence that infection prolongs wound healing. Therefore, there is the need to distinguish between bacterial colonization of the wound and true infection that actually compromises the tissue [1].

## **14. The use of silver and iodine to control wound infection**

Many dressings incorporate compounds such as silver and iodine to control infection. Silver is an anion with strong antimicrobial activity. Therefore, it has been used for decades to treat wound infections. The mechanism by which silver ions kill microorganisms is by inhibiting bacterial-specific enzymes that are important in bacterial cell wall synthesis and gene transcription. There is evidence that silver-containing dressings considerably decrease the

incidence of burn wound –associated sepsis and bacteremia as well as shorten hospitalization time. Additionally, silver ions reduce the levels of matrix metalloproteinases that are upregulated in non-healing wounds [28].

## 15. Silver-containing dressings

At the original introduction of silver-containing dressings, silver ions were present in the form of silver nitrate and silver sulfadiazine. However, newer formulations are composed of high density polyethylene mesh that is impregnated with nanocrystalline silver. Acticoat, Actisorb Silver, Contreet Foam, Contreet Hydrocolloid and Silverlon and examples of nanocrystalline silver dressings [45].

These dressings offer antibiotic activity against both gram-positive and gram-negative bacteria. Each of these dressings is able to release antibacterial levels of silver for 3–7 days. Research has indicated that silver impregnated dressings can enhance the short-term healing of wounds and ulcers [1].

However, recent studies have shown, that in certain patient populations, the use of silver-containing dressings is contraindicated due to potential toxicity. These include, patients with surgical wounds that are at low risk for infection, pregnant or lactating women, patients who are sensitive or allergic to silver or metals, patients with wounds being treated with an enzymatic debridement agent, patients with wounds that have no signs and symptoms of infection present, chronic wounds that are healing as expected, patients with wounds in or near sites that are being treated or have been treated with radiotherapy, patients with wounds in which slough or necrotic tissue is present, as well as wounds that are colonized with multiple organisms or biofilms [46].

Additionally, there have been reports of silver toxicity in the setting of treating large-surface-area wounds with silver impregnated dressings. Therefore, silver toxicity should be considered when patients present with leukopenia [47].

## 16. Use of iodine in wound dressing

Iodine has been used to help with wound healing for over 150 years [48]. Povidone-iodine is a frequently used antiseptic which can actually inhibit wound healing [49]. However, there are newer dressings, such as cadexomer-iodine polymer that slowly release iodine from dextran beads. These do not appear to have toxic effects on keratinocytes. In this dressing, there is a low level of iodine that is slowly released from the beads.

Iodine wound dressings are recommended for exudative wounds, including leg ulcers and are not appropriate in the treatment of autoimmune bullous disease. Caution must be taken when using these dressings in patients with a history of thyroid disease. These dressings should be avoided in young children, pregnant or lactating women or patients with a known or suspected iodine insensitivity [49].

## 17. Recommended wound care in immunobullous disease

### 17.1. Treatment of pemphigus vulgaris, pemphigoid and Steven Johnson syndrome in a burn unit

Steven-Johnsons syndrome, toxic epidermal necrosis, pemphigus vulgaris and bullous pemphigoid display disruption of the skin layers or its blood supply and produce similar lesions that mimic a burn injury. When greater than 60% of total body surface area is involved, it is recommended that patients are admitted to a burn care unit. In the unit, these patients are provided with a proper environment, temperature, humidity and infrared lamps to prevent infection. High mortality and morbidity are reduced by proper handling and hospitalization in a burn care unit. Wound management in these diseases require similar care to burns, as well as fluid resuscitation and dietary care [50].

### 17.2. General nursing care pemphigus and pemphigoid

The best approach to the care of blistered skin has not yet been definitively established. There is currently controversy on how to deal with small tense blisters. While some resources recommend daily rupturing of tense blisters for reducing lateral extension of the blister edges, other resources advocate for leaving blisters intact, to prevent secondary infection. However, large blisters should be aspirated with a sterile needle, to keep the blister roof in place. Raw areas need to be cleaned by antiseptics or normal saline and then covered by a non-adhesive dressing. Excessive skin manipulation and trauma should be avoided in active pemphigus vulgaris [51]. When patients have oral mucosal lesions, it is recommended them to maintain a soft diet, use soft tooth brushes, antiseptic gargles and prophylaxis against oral candidiasis [52].

The wound care in treating pemphigus vulgaris and bullous pemphigoid depends on the severity of the disease, the location of the lesions, as well as the total body surface area (TBSA) covered with lesions. While there have been several case studies published with different recommendations regarding wound care, each is individualized to the unique needs of the specific patient, and there is not yet one specific standard of care [52].

When patients who have extensive raw areas are hospitalized, they must be isolated to reduce cross-infection. Secondary bacterial (MRSA, pseudomonas) or viral (HSV) infections can occur. The use of antimicrobials is effective. Additionally, it is important to routinely monitor blood pressure and blood glucose levels. Steroid related complications frequently occur shortly or within 1 year of the start of systemic treatment in bullous pemphigoid. These include infection, worsening of diabetes or blood pressure, and pressure sores. These complications must be monitored so that the immunosuppressant dose can be adjusted if needed [53]. After prolonged hospitalization, MRSA colonization can occur. Additionally, a five-day decontamination regime with 4% chlorhexidine body wash and nasal mupirocin ointment may be considered when lesions resolve [51].

Typically, hospitalized patients with bullous pemphigoid have multiple comorbidities, and often present with generalized involvement, a more severe disease, recurrent relapses, higher morbidity and mortality. This occurs especially in the first year. Patients typically have a worse prognosis when they are bed bound, anemic, hypoalbuminemic or have a malignancy [51].



### 17.3. Severe disease

In severe disease, the premise of care is very similar to patients being treated for partial thickness burn therapy. Frequently in pemphigus vulgaris and bullous pemphigoid, the body is covered with intact bullae and partial-thickness wounds from head to toe. Serous sanguineous fluid drains onto the linens, which exacerbates pain since once it dries it becomes stuck and unstuck to bed sheets and bandages [54] (**Figure 7**).

In severe pemphigus and pemphigoid, various goals of wound care management have been identified. These include relieving severe pain, preventing infection and decreasing bioburden, enhancing regeneration of the dermis and the epidermis, protecting the periwound skin from maceration, encouraging patient mobility and quality of life, providing nutritional support for tissue repair, as well as treating the underlying cause of the wound [55].

All dressing products used for these patients must be nonadherent. Following chemotherapy for severe lymphocytic leukemia, a 66 year old female with pemphigus vulgaris was given a daily dressing which utilized a foaming skin care wash [56]. Additionally, there was a non-sting barrier to protect the intact skin and hydrogel sheets to provide a moist environment. An advanced ionized silver wound-care product in the form of a gel or powder was considered given the possibility of wound infection. Xerofoam gauze is an optimal product to add over the hydrogel sheet to prevent it from drying out and to stabilize it. At the start of the wound care, large abdominal dressings were also applied over the Xerofoam gauze to absorb the drainage. Above that, various kinds of stretch bandages or nets were placed to secure the



**Figure 7.** Pemphigus vulgaris lesions on patient's leg.

dressing [54]. It is important to keep the skin surface moist and not open to air for healing and pain management.

Ultimately, the wound care plan focuses on reducing pain, preventing infection by gentle cleansing and preventing scarring by providing a moist environment. Additionally, nutrition is a key aspect of care, due to the loss of protein and other essential components in the serous sanguineous drainage [51] (**Table 3**).

**17.4. Silver containing hydrofiber dressings for pemphigus vulgaris wounds**

Recent studies have advocated for the use of silver-containing hydrofiber dressings as effective adjunct in the treatment of pemphigus vulgaris. Following the application of these dressings,

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1. Clean the wound
a. Use a foaming skin care wash (Cetaphil or Cerave)
i. allows cleaning of the wound without pain, it is nonabrasive
a. Apply directly to wounds and then gently rinse off
b. Shower
c. Wrap in a warm bath blanket to maintain temperature, which is conducive to wound healing
2. Protect the periwound skin
a. "No-sting" skin barrier similar to applying a thin film on the intact skin as a shield against excessive moisture
a. No-sting is painless because alcohol is not an ingredient
i. Spray (StingFree)
ii. Pad (StingFree)
3. Provide a moist environment
a. Hydrogel sheet
i. Gelled water formed into a flat dressing
ii. 4 × 4 or 6 × 8 inches
b. Cover wound with film with the sticky side placed on the wound bed
4. Optional step: placement of a fine mesh nonadherent gauze which is impregnated with petrolatum and 3% bismuth tribomophenate
a. the gauze secures the hydrogel and provides additional protection of the periwound skin
5. Optional step: If wound drainage is excessive, then heavy ABD pads (cotton dressing pads) can be applied to wick away the drainage
6. Secure dressing with Kerlix, a conforming, 100% woven gauze
7. A self-adhesive wrap with minimal stretch provides the finishing touch to the dressing, allowing the patient mobility and improved quality of life

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**Table 3.** Wound care plan [55].

there was marked improvement in wound healing and decreased patient discomfort [45]. Additionally, topical measures such as hydrotherapy, topical glucocorticoids and topical antimicrobial agents also help to control the disease. Unfortunately, some patients are resistant to these conventional therapies. Previous studies have supported the use of silver containing hydrofiber dressing patches (SHD) for managing partial thickness burns and toxic epidermal necrolysis [45].

SHD is made from the hydrocolloid polymer carboxymethylcellulose to which silver ions are attached. The dressing fibers absorb wound exudate and swell to form a soft cohesive gel that covers the wound surface. It has the ability to absorb large volumes of exudate, up to 20 times its weight in fluid. Therefore, it is suitable for heavy exudating wounds. Since it retains fluid in the dressing over the wound, it dehydrates less quickly than other dressings and promotes a moist healing environment. Additionally, it limits lateral movement of fluid and avoids maceration of the surrounding skin [45].

A recent case of pemphigus vulgaris involving 62% of the total body surface area (TBSA), examined the effectiveness of SHD for wound healing [45]. Following the use of SHD, the patient showed dramatic wound healing with reduced patient discomfort. Specifically, after starting the SHD therapy, there was a marked improvement in wound healing and the affected TBSA decreased from 62–5% over just 4 weeks. After just 1 week after starting the SHD therapy, no new skin lesions were noted. Not only did this treatment appear to be effective in wound healing, but it is also less time consuming. Dressing changes only took 45 minutes every 3 days with SHD, compared with 2 hours every day with hydrotherapy and SSD care. It was also noted that the patient experienced less pain and discomfort during the dressing changes.

### **17.5. The use of nano-silver dressings (Acticoat) in pemphigus vulgaris**

As stated above, over the past three decades, nanocrystalline silver dressings have provided antimicrobial, pro-healing, and anti-inflammatory activity. Antibacterial effects have minimized the frequency of wound dressing and have improved the healing of acute and chronic lesions from superficial to deep layers. Acticoat is a silver biologic dressing containing a 15 nm bactericidal coat of nanocrystallized ions of silver in a cluster structure. It coats many cells that are exposed to infection and protects them through continuous silver ion release. Acticoat is able to eliminate at least 150 types of microorganisms after 30 min of use. Nanocrystalline skin dressings have been found to be beneficial in many skin lesions, including burns. It has also been found that compared with traditional wound dressings such as silver sulfadiazine, nanocrystalline coated silver dressings not only have shortened hospital stays and less frequency of wound dressing changes, but there is also improved wound healing and balancing overall costs, in addition to a higher satisfaction rate by patients [57].

Masjedi et al. compared a nanocrystalline silver dressing with a regular sulfadiazine normal dressing (the control) in the treatment of pemphigus vulgaris lesions [58]. 16 patients each received both an experimental and control dressing on symmetrical lesions. Qualitative wound score (QWS) and clinical photography were conducted during treatment for 4 weeks. After 4 weeks, QWS decreased by 1.94 more in the experimental compared to baseline than in

the control group. Ultimately, after 4 weeks, QWS decreased by 1.95 more in the experimental compared to baseline than in the control group. Additionally, after 4 weeks, Acticoat showed complete healing in 13 cases in addition to one acceptable healing. It was also noted that Acticoat shortened hospital stay and provided easier handling. While this study showed that the nanocrystalline silver dressing, Acticoat was superior to the silver sulfadiazine dressing in treating vesicobullous lesions, there still has not been a trial which examined the effect of this dressing on wound healing time without superinfection and on costs and complications.

#### **17.6. The use of banana leaf for wound management of patients with toxic epidermal necrolysis**

Steven Johnsons Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are life-threatening allergic reactions usually to medications, which require immediate treatment. These two diseases can be differentiated by the surface area affected by epidermal necrosis. SJS only involves skin lesions on less than 10% of the total body surface area, whereas TEN involves 10–30% skin lesions with severe inflammation of mucosal tissues.

The main goal is to prevent infection and to encourage healing. Wound care for these diseases is similar to severe cases of pemphigus vulgaris and bullous pemphigoid.

Modern medical supplies for wound management include paraffin coated mesh, Vaseline, petroleum, disinfectant dressings with silver-compounds such as nanocrystalline silver dressing, silver hydrofiber, as well as silicone silver foam dressing. These dressings are all very expensive, and efforts must be made to find dressings, which reduce cost as well as pain level.

Recent studies have found that using aloe vera resulted in better healing rate than silver sulfadiazine (SSD) [59]. Additional studies have explored using honey dressing on burns and found that they resulted in better healing and lower rate of necrosis compared to SSD [60]. In a comparative study between boiled potato peel bandages and sterile banana leaf, there were similar healing rates between the two, but the banana leaf was more cost effective and did not cling to the wound as much [61].

Uppanisakorn et al. examined the use of a sterile banana leaf dressing, which allowed the patient to be discharged swiftly and reduced the cost of treatment by eight times. When supportive therapy using banana leaf dressing was given, the patient was able to be discharged within 12 days [62].

There is much promise in the use of sterile banana leaf dressings for wound management. The price is 160 times lower than the cost of paraffin gauze. It has also been known to decrease pain and increase ease and speed of wound healing. The only caution of using banana leaf dressings is the potential for infection from contamination.

Further research must be done to determine the efficacy of banana leaf dressings for patients with pemphigus and pemphigoid.

#### **17.7. Pemphigoid wound care – specific considerations**

Pemphigoid most frequently affects elderly adults. As a result, these patients are frequently dependent upon relatives or health care workers for personal care activities. Therefore, their



ability to comply with treatment must be considered. Topical corticosteroid therapy is not a favorable option for patients who are unable to properly apply the medication and lack access to assistance. In this patient population, a combination of comorbidities and adverse effects of treatment, rather than the direct effects of disease, are what actually lead to morbidity and mortality. Treatment should be conservative and a minimal amount of medication required to achieve remission should be given [50].

While a high potency topical corticosteroid is often used for patients with bullous pemphigoid, if the patients are unable to properly administer topical treatment, a systemic glucocorticoid will be required. These are typically more accessible to patients at a lower cost, and have increased compliance. In addition, often when patients have widespread involvement, systemic therapy is faster and easier to administer than topical therapy [63].

### 17.8. Mucosal wound care

Oral blisters in pemphigus vulgaris have a very thin roof and rupture as a result of oral traumas, which leads to multiple chronic painful bleeding ulcers and erosions that heal with difficulty (**Figure 8**). There are patient reports of pain in the oral cavity as well as a burning sensation that occurs when they consume spicy or acidic foods. While blisters can appear at any localization of the oral mucosa, they most frequently appear in sites that are subjected to friction, including the soft palate, buccal mucosa, ventral tongue, gingiva, and lower lip. Infrequently, there are lesions on the gingiva [64]. In more advanced stages of pemphigus vulgaris, desquamative or erosive gingivitis can be observed. There are other oral manifestations, including sialorrhea, halitosis and the continuous formation of brown or blackish crusts at the vermillion border. Pemphigus vulgaris can involve the conjunctiva, nasal, pharyngeal, laryngeal, esophageal, genital and anal mucosa as well. Blisters typically rupture more easily on the mucosa than on the skin [64].

Oral lesions present a challenge, give their slow response to treatment in comparison to cutaneous lesions. When patients have low titers of circulating antibodies, lesions can be



**Figure 8.** Patient with pemphigus vulgaris in the oral mucosa.



controlled temporarily with mouthwashes or topical creams that contain corticosteroids. These include 0.1% triamcinolone acetonide in orabase, 0.05% fluocinolone acetonide, 0.05% clobetasol propionate, or 0.05% halobetasol. Intralesional injection of triamcinolone acetonide (20 µg/L) or paramethasone every 5–15 days can be used in refractory lesions. However, the treatment should be withdrawn if symptoms do not improve after three injections [64].

To improve the wellbeing of patients suffering from mucosal lesions, it is recommended to administer analgesics, maintain oral hygiene using diluted antiseptic (chlorohexidine) mouthwashes, periodontal treatment, following a soft diet without irritants, checking prosthetic restorations, and applying anti-candida therapy in patients on long-term corticosteroid treatments [64].

Since oral trauma can trigger or worsen pemphigus vulgaris, Bystrn et al. recommended the prophylactic administration of 20 mg prednisone/day in addition to the patient's normal requirement for 5–7 days before any dental procedure that is associated with trauma to the gums [2].

The nostrils should be cleaned daily with a sterile cotton swab that is moistened with isotonic sterile sodium chloride solution. Antibiotic ointment should also be applied to the nostrils. The mouth should be rinsed a few times a day using a syringe with isotonic sterile sodium chloride solution [2].

## 18. Conclusion

There is current controversy on how to achieve optimal wound management of this disease. When the disease becomes severe, patients are typically admitted to the burn unit. Therefore, the supportive care resembles that performed for severe thermal burns TEN. It aims at minimizing potential complications which may ultimately lead to patient mortality. For instance, it aims to avoid hypovolemia, electrolyte imbalance, renal insufficiency and sepsis [24].

Careful wound care, hydration and nutritional support are critical and performed in an intensive care unit if there is epidermal detachment involving 10–20% or more of body surface area. Current wound care recommendations include using controlled pressure as well as thermoregulated bed and sheets. It is essential for all procedures to occur in a sterile environment and for venous catheters to only be placed in regions of non-involved skin [65].

It is advised that wound care be performed under the guidance of a dermatologist, due to the complex issues these patients face. Cutaneous care should include the face, eyes, nose, mouth, ear, anogenital region, axillary folds and interdigital spaces. When cutaneous areas are non-detached, they must be kept dry and not manipulated. However, detached cutaneous areas should be covered with Vaseline gauze until reepithelization has occurred [24].

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## References

- [1] Bologna J, Schaffer JV, Duncan KO, Ko CJ. *Dermatology Essentials*. Oxford: Saunders/Elsevier; 2014
- [2] Bystryn JC, Rudolph JL. Pemphigus. *Lancet*. 2005;**366**(9479):61-73. DOI: 10.1016/s0140-6736(05)66829-8
- [3] Murrell DF, Dick S, Ahmed AR, Amagai M, Barnadas MA, Borradori L, et al. Consensus statement on definitions of disease, end points, and therapeutic response for pemphigus. *Journal of the American Academy of Dermatology*. 2008;**58**(6):1043-1046. DOI: 10.1016/j.jaad.2008.01.012
- [4] Hammers CM, Stanley JR. Mechanisms of disease: Pemphigus and bullous pemphigoid. *Annual Review of Pathology*. 2016;**11**:175-197. DOI: 10.1146/annurev-pathol-012615-044313
- [5] Amagai M. Autoimmune and infectious skin diseases that target desmogleins. *Proceedings of the Japan Academy. Series B, Physical and Biological Sciences*. 2010;**86**(5):524-537. DOI: 10.2183/pjab.86.524
- [6] Sitaru C, Mihai S, Zillikens D. The relevance of the IgG subclass of autoantibodies for blister induction in autoimmune bullous skin diseases. *Archives of Dermatological Research*. 2007;**299**(1):1-8. DOI: 10.1007/s00403-007-0734-0
- [7] Xu H-H, Werth VP, Parisi E, Sollecito TP. Mucous membrane pemphigoid. *Dental Clinics of North America*. 2013;**57**(4):611-630. DOI: 10.1016/j.cden.2013.07.003
- [8] Mehren CR, Gniadecki R. Epidermolysis bullosa acquisita: Current diagnosis and therapy. *Dermatology Reports*. 2011;**3**(3):e38. DOI: 10.4081/dr.2011.e38
- [9] Gregoriou S, Efthymiou O, Stefanaki C, Rigopoulos D. Management of pemphigus vulgaris: Challenges and solutions. *Clinical, Cosmetic and Investigational Dermatology*. 2015;**8**:521-527. DOI: 10.2147/CCID.S75908
- [10] Tamgadge S, Tamgadge A, Bhatt DM, Bhalerao S, Pereira T. Pemphigus vulgaris. *Contemporary Clinical Dentistry*. 2011;**2**(2):134-137. DOI: 10.4103/0976-237X.83074

- [11] Pires CAA, Viana VB, Araújo FC, Müller SFR, de Oliveira MS, Carneiro FRO. Evaluation of cases of pemphigus vulgaris and pemphigus foliaceus from a reference service in Pará state, Brazil. *Anais Brasileiros de Dermatologia*. 2014;**89**(4):556-561. DOI: 10.1590/abd1806-4841.20142679
- [12] Schmidt E, Zillikens D. The diagnosis and treatment of autoimmune blistering skin diseases. *Deutsches Ärzteblatt International*. 2011;**108**(23):399-405. DOI: 10.3238/arztebl.2011.0405
- [13] Neff AG, Turner M, Mutasim DF. Treatment strategies in mucous membrane pemphigoid. *Therapeutics and Clinical Risk Management*. 2008;**4**(3):617-626
- [14] Murrell DF, Daniel BS, Joly P, Borradori L, Amagai M, Hashimoto T, et al. Definitions and outcome measures for bullous pemphigoid: Recommendations by an international panel of experts. *Journal of the American Academy of Dermatology*. 2012;**66**(3):479-485. DOI: 10.1016/j.jaad.2011.06.032
- [15] Zheng Z, Nguyen C, Zhang X, Khorasani H, Wang JZ, Zara JN, et al. Delayed wound closure in fibromodulin-deficient mice is associated with increased TGF- $\beta$ 3 signaling. *The Journal of Investigative Dermatology*. 2011;**131**(3):769-778. DOI: 10.1038/jid.2010.381
- [16] Anderson K, Hamm RL. Factors that impair wound healing. *The Journal of the American College of Clinical Wound Specialists*. 2012;**4**(4):84-91. DOI: 10.1016/j.jccw.2014.03.001
- [17] Song F, Li B, Stocum DL. Amphibians as research models for regenerative medicine. *Organogenesis*. 2010;**6**(3):141-150
- [18] Stewart S, Stankunas K. Limited dedifferentiation provides replacement tissue during Zebrafish fin regeneration. *Developmental Biology*. 2012;**365**(2):339-349. DOI: 10.1016/j.ydbio.2012.02.031
- [19] Hasegawa T, Hall CJ, Crosier PS, Abe G, Kawakami K, Kudo A, Kawakami A. Transient inflammatory response mediated by interleukin-1 $\beta$  is required for proper regeneration in zebrafish fin fold. *eLife*. 2017;**6**:e22716. DOI: 10.7554/eLife.22716
- [20] Yates CC, Hebda P, Wells A. Skin wound healing and scarring: Fetal wounds and regenerative restitution. *Birth Defects Research. Part C, Embryo Today : Reviews*. 2012;**96**(4):325-333. DOI: 10.1002/bdrc.21024
- [21] Larson BJ, Longaker MT, Lorenz HP. Scarless fetal wound healing: A basic science review. *Plastic and Reconstructive Surgery*. 2010;**126**(4):1172-1180. DOI: 10.1097/PRS.0b013e3181eae781
- [22] Torricelli AAM, Singh V, Santhiago MR, Wilson SE. The corneal epithelial basement membrane: Structure, function, and disease. *Investigative Ophthalmology & Visual Science*. 2013;**54**(9):6390-6400. DOI: 10.1167/iovs.13-12547
- [23] Saparov A, Chen C-W, Beckman SA, Wang Y, Huard J. The role of antioxidation and immunomodulation in postnatal multipotent stem cell-mediated cardiac repair. *International Journal of Molecular Sciences*. 2013;**14**(8):16258-16279. DOI: 10.3390/ijms140816258

- [24] Donners MMPC, Bai L, Lutgens SPM, Wijnands E, Johnson J, Schurgers LJ, et al. Cathepsin K deficiency prevents the aggravated vascular Remodeling response to flow cessation in ApoE(−/−) mice. *PLoS One*. 2016;**11**(9):e0162595. DOI: 10.1371/journal.pone.0162595
- [25] Chadwick SL, Yip C, Ferguson MWJ, Shah M. Repigmentation of cutaneous scars depends on original wound type. *Journal of Anatomy*. 2013;**223**(1):74-82. DOI: 10.1111/joa.12052
- [26] Rittié L. Cellular mechanisms of skin repair in humans and other mammals. *Journal of Cell Communication and Signaling*. 2016;**10**(2):103-120. DOI: 10.1007/s12079-016-0330-1
- [27] Grim SA, Slover CM, Sankary H, Oberholzer J, Benedetti E, Clark NM. Risk factors for wound healing complications in sirolimus-treated renal transplant recipients. *Transplantation Proceedings*. 2006;**38**(10):3520-3523. DOI: 10.1016/j.transproceed.2006.10.065
- [28] Yang JY, Huang CY, Chuang SS, Chen CC. A clinical experience of treating exfoliative wounds using nanocrystalline silver-containing dressings (Acticoat). *Burns*. 2007;**33**(6):793-797. DOI: 10.1016/j.burns.2006.11.010
- [29] Pastar I, Stojadinovic O, Yin NC, Ramirez H, Nusbaum AG, Sawaya A, et al. Epithelialization in wound healing: A comprehensive review. *Advances in Wound Care*. 2014;**3**(7):445-464. DOI: 10.1089/wound.2013.0473
- [30] Hunt TK, Dunphy JE. *Fundamentals of Wound Management*. New York: Appleton Century Crofts; 1979
- [31] Winter GD. Formation of the scab and the rate of epithelization of superficial wounds in the skin of the young domestic pig. *Nature*. 1962;**193**:293-294
- [32] Gannon HS, Donehower LA, Lyle S, Jones SN. Mdm2-p53 signaling regulates epidermal stem cell senescence and premature aging phenotypes in mouse skin. *Developmental Biology*. 2011;**353**(1):1-9. DOI: 10.1016/j.ydbio.2011.02.007
- [33] Bootun R. Effects of immunosuppressive therapy on wound healing. *International Wound Journal*. 2013;**10**(1):98-104. DOI: 10.1111/j.1742-481X.2012.00950.x
- [34] Burgos FJ, et al. Post-kidney transplant surgical complications under new immunosuppressive regimens. *Transplantation Proceedings*. 2006;**38**(8):2445-2447
- [35] Valente JF, et al. Comparison of sirolimus vs. mycophenolate mofetil on surgical complications and wound healing in adult kidney transplantation. *American Journal of Transplantation*. 2003;**3**(9):1128-1134
- [36] Selman SM, et al. Rituximab delays wound healing and decreases white blood cell count in male mice. 2017;**2017**:5
- [37] Fauci AS. Corticosteroids in autoimmune disease. *Hospital Practice (Office Ed.)*. 1983;**18**(10):99-103, 107-118, 113-104
- [38] Guo S, DiPietro LA. Factors affecting wound healing. *Journal of Dental Research*. 2010;**89**(3):219-229. DOI: 10.1177/0022034509359125

- [39] Eaglstein WH, Davis SC, Mehle AL, Mertz PM. Optimal use of an occlusive dressing to enhance healing. Effect of delayed application and early removal on wound healing. *Archives of Dermatology*. 1988;**124**(3):392-395
- [40] Kaigler D, Avila G, Wisner-Lynch L, Nevins ML, Nevins M, Rasperini G, et al. Platelet-derived growth factor applications in periodontal and peri-implant bone regeneration. *Expert Opinion on Biological Therapy*. 2011;**11**(3):375-385. DOI: 10.1517/14712598.2011.554814
- [41] Wankell M, Munz B, Hübner G, Hans W, Wolf E, Goppelt A, Werner S. Impaired wound healing in transgenic mice overexpressing the activin antagonist follistatin in the epidermis. *The EMBO Journal*. 2001;**20**(19):5361-5372. DOI: 10.1093/emboj/20.19.5361
- [42] Werner S, Grose R. Regulation of wound healing by growth factors and cytokines. *Physiological Reviews*. 2003;**83**(3):835-870. DOI: 10.1152/physrev.00031.2002
- [43] Li W, Dasgeb B, Phillips T, Li Y, Chen M, Garner W, Woodley DT. Wound-healing perspectives. *Dermatologic Clinics*. 2005;**23**(2):181-192. DOI: 10.1016/j.det.2004.09.004
- [44] Sood A, Granick MS, Tomaselli NL. Wound dressings and comparative effectiveness data. *Advances in Wound Care*. 2014;**3**(8):511-529. DOI: 10.1089/wound.2012.0401
- [45] Wu CS, Hsu HY, Hu SC, Chiu HH, Chen GS. Silver-containing hydrofiber dressing is an effective adjunct in the treatment of pemphigus vulgaris. *The Kaohsiung Journal of Medical Sciences*. 2009;**25**(11):622-627. DOI: 10.1016/S1607-551X(09)70567-4
- [46] Leaper D. Appropriate use of silver dressings in wounds: International consensus document. *International Wound Journal*. 2012;**9**(5):461-464. DOI: 10.1111/j.1742-481X.2012.01091.x
- [47] LaRiviere CA, Goldin AB, Avansino J. Silver toxicity with the use of silver-impregnated dressing and wound vacuum-assisted closure in an immunocompromised patient. *The Journal of the American College of Certified Wound Specialists*. 2011;**3**(1):8-12. DOI: 10.1016/j.jcws.2011.05.002
- [48] Cooper RA. Iodine revisited. *International Wound Journal*. 2007;**4**(2):124-137. DOI: 10.1111/j.1742-481X.2007.00314.x
- [49] Goldenheim PD. An appraisal of povidone-iodine and wound healing. *Postgraduate Medical Journal*. 1993;**69**(Suppl 3):S97-105
- [50] Castana O, Makrodinou M, Michelakis D, Tsandoulas Z, Alexakis D. Diseases mimicking a burn - outcome and treatment. *Annals of Burns and Fire Disasters*. 2005;**18**(3):130-132
- [51] Brandão EDS, dos Santos I, Lanzillotti RS, Ferreira AM, Gamba MA, Azulay-Abulafia L. Nursing diagnoses in patients with immune-bullous dermatosis. *Revista Latino-Americana de Enfermagem*. 2016;**24**:e2766. DOI: 10.1590/1518-8345.0424.2766
- [52] Fishman TD. Wound assessment and evaluation...Bullous pemphigoid. *Dermatology Nursing*. 1999;**11**(6):436-437



- [53] McCuin JB, Hanlon T, Mutasim DF. Autoimmune bullous diseases: Diagnosis and management. *Dermatology Nursing*. 2006;**18**(1):20-25
- [54] Miletta N, Miller ME, Lam T, Chung KK, Hivnor C. The management of pemphigus vulgaris in a burn intensive care unit: A case report and treatment review. *Journal of Burn Care & Research*. 2014;**35**(5):e357-e363. DOI: 10.1097/bcr.0000000000000049
- [55] Blackett AV. Managing Painful Surface Wounds. *Oncology(Oncology Nursing, Palliative and Supportive Care)*; 2007
- [56] Hayanga AJ, Lee TM, Pannucci CJ, Knipp BS, Olsen SH, Wang SC, Napolitano LM. Paraneoplastic pemphigus in a burn intensive care unit: Case report and review of the literature. *Journal of Burn Care & Research*. 2010;**31**(5):826-829. DOI: 10.1097/BCR.0b013e3181eed4b4
- [57] Masjedi H. The healing effects of nano-silver dressings in pemphigus vulgaris. *Wounds Middle East*. 2015;**2**(3):33-37
- [58] Masjedi H. In: Malekzad F, editor. *The Healing Effect of Nano-Silver Dressings in Pemphigus Vulgaris*. Vol. 2. Tehran, Iran: Wounds Middle East; 2015. p. 6
- [59] Khorasani G, Hosseinimehr SJ, Azadbakht M, Zamani A, Mahdavi MR. Aloe versus silver sulfadiazine creams for second-degree burns: A randomized controlled study. *Surgery Today*. 2009;**39**(7):587-591. DOI: 10.1007/s00595-008-3944-y
- [60] Baghel PS, Shukla S, Mathur RK, Randa R. A comparative study to evaluate the effect of honey dressing and silver sulfadiazene dressing on wound healing in burn patients. *Indian Journal of Plastic Surgery: Official Publication of the Association of Plastic Surgeons of India*. 2009;**42**(2):176-181. DOI: 10.4103/0970-0358.59276
- [61] Jurjus A, Atiyeh BS, Abdallah IM, Jurjus RA, Hayek SN, Jaoude MA, et al. Pharmacological modulation of wound healing in experimental burns. *Burns*. 2007;**33**(7):892-907. DOI: 10.1016/j.burns.2006.10.406
- [62] Uppanisakorn S, Boonyarat J. Wound management of patients with toxic epidermal necrolysis using banana leaf: A case study. *Advanced Practices in Nursing*. 2017;**02**
- [63] Venning VA, Taghipour K, Mohd Mustapa MF, Highet AS, Kirtschig G. British Association of Dermatologists' guidelines for the management of bullous pemphigoid 2012. *British Journal of Dermatology*. 2012;**167**(6):1200-1214. DOI: 10.1111/bjd.12072
- [64] Arpita R, Monica A, Venkatesh N, Atul S, Varun M. Oral pemphigus vulgaris: Case report. *Ethiopian Journal of Health Sciences*. 2015;**25**(4):367-372
- [65] Khalili B, Bahna SL. Pathogenesis and recent therapeutic trends in Stevens-Johnson syndrome and toxic epidermal necrolysis. *Annals of Allergy, Asthma & Immunology*. 2006;**97**(3):272-280; quiz 281-273, 320. DOI: 10.1016/s1081-1206(10)60789-2

